

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 47/34	A1	(11) International Publication Number: WO 99/40943 (43) International Publication Date: 19 August 1999 (19.08.99)
(21) International Application Number: PCT/US98/19750 (22) International Filing Date: 22 September 1998 (22.09.98) (30) Priority Data: 980115 16 February 1998 (16.02.98) IE (71) Applicant: FUISZ INTERNATIONAL LTD. [IE/US]; 14555 Avion at Lakeside, Chantilly, VA 20151 (US). (72) Inventor: BOGUE, B., Arlie; 6360 Cotswold Bay, Broad Run, VA 20137 (US). (74) Agents: NOLAN, Sandra, M. et al.; Fuisz Technologies Ltd., 14555 Avion at Lakeside, Chantilly, VA 20151 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TF, UA, UG, UZ, VN, YU, ZW, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: SOLUBILIZING DELIVERY SYSTEMS AND METHOD OF MANUFACTURE (57) Abstract <p>Active agent/surfactant combinations are blended using selected processing conditions to at least partially place a eutectic of the combinations into intimate contact with particles of the active. The blending process enhances the solubility of the actives while allowing higher concentrations of active to be solubilized at rates than were previously possible.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

SOLUBILIZING DELIVERY SYSTEMS AND METHOD OF MANUFACTURE

Field of the Invention

The invention relates to solubilizing delivery systems in which poorly soluble materials therein dissolve readily in aqueous solutions and processes for their manufacture. More particularly the solubilizing delivery systems are combinations of an active agent/solubilizer eutectic composition in intimate contact with particles of the active agent. When active agents are pharmaceutical materials or drugs the solubilizing delivery system products may thereafter be combined with suitable amounts of conventional pharmaceutical ingredients to make comestible units or oral dosage forms, such as tablets or capsules.

Background

The preparation of drug/polymer combinations where the drug is combined with a melt of a polymer is known. These preparations include such concepts as melt mixing and extrusion.

Drugs have been blended with molten surfactants or dispersions of surfactants in order to produce solid solutions of drugs in surfactants. PCT application WO 97/02017, published January 23, 1997, shows the use of molten Pluronic surfactants as a dissolution aid for various drugs, including ibuprofen, in controlled release formulations. In the melt-blending operation disclosed therein, the drug was added to the surfactant at a temperature above the surfactant's melting point.

In literature dated 1994 and 1997, BASF Corporation discloses the production of melt extruded drug/polymer products, however no particulars of their preparation are disclosed.

In an abstract entitled "Application of Bridging Agents to Produce an Ibuprofen-Xylitol Solid Dispersion System", Greenhalgh et al. disclose the use of a Pluronic surfactant to overcome the immiscibility of ibuprofen in xylitol. They teach and disclose ibuprofen and Pluronic F68 mixtures as forming a eutectic substance having a melting point at 38°C.

According to an abstract of an article entitled "Compatibility of Ibuprofen and Ethenzamide", Drug Development and Industrial Pharmacy, Vol. 23, No. 6, 1997, pp 561-565, the chemical stability of ibuprofen and various drugs was investigated. The investigators reported that a eutectic was formed between ibuprofen and ethenzamide. In addition they reported that the chemical stability of that eutectic (with small amounts of excipients) in capsule form was found to be stable. The investigators also reported that a "remarkable" delay in dissolution was noted when the eutectic was formed above 56°C (the eutectic's melting point.)

These disclosures, however, fail to recognize, or teach the reasons for delayed dissolution of drug/ polymer (solubilizer) eutectics processed above their eutectic formation temperatures. Nor do they teach that such drug/ polymer (solubilizer) eutectics, while improving solubility of the drug, do not allow one to produce finished, marketable drug products due to the low "loading" capacity of the solubilizer, i.e., the solubilizer can only be "loaded" with relatively small amounts of active before adverse dissolution properties again come into play. Such a low "loading" of active results in oversized dosage forms to be able to deliver a sufficient amount of the active to the patient. Therefore, a need exists for high "load" drug delivery systems while still utilizing the enhanced solubilizing properties of solubilizers and surface acting agent combinations.

20 Summary of the Invention

The invention relates to solubilizing delivery systems and the method of producing them wherein particles of at least one active agent and at least one solubilizing agent, such as surface active agents (solubilizer), are processed at low temperatures, i.e., at temperatures below the melting points of both, and preferably from below the formation temperature of a eutectic of the active and solubilizer combination to below the temperature at which the active dissolves in the solubilizer. The processing further involves combining of ingredients at the above stated processing temperatures in the presence of forces sufficient to produce a active/solubilizer eutectic which is at least partially coated onto, or in intimate contact with, particles of the active. Preferably the particles are a crystalline form of the active ingredient at least partially surrounded or enveloped by a eutectic mixture of the active and solubilizer(s). The eutectic may also

contain crystals of the active. In the case of actives intended to be absorbed in the gut, such as Ibuprofen, the solubilizing/active systems produced by this invention have superior aqueous solubility at pH 5.2 compared to the active alone and contain from about 10% to about 95% active, and preferably from about 30% to about 90% active, and most preferably from about 40% to about 80% active.

Applicant has found that certain actives, and especially drugs will form a eutectic material with certain solubilizers when processed under sufficient forces (such as shear forces, centrifugal forces or pressure) and at temperatures from below the formation temperature of the eutectic to below the temperature at which the active dissolves in the solubilizer, or melts. These eutectics, while in the presence of the temperature and force, will coat or envelop, at least partially, particles of the active (solubilizing delivery system). This solubilizing delivery system contains a higher percentage of active than the eutectic alone is capable of while still retaining the enhanced dissolution properties of the eutectic or a combination product of the solubilizer and active. The resulting product may then be further processed (such as milling) to produce microparticles which may in turn be further processed into dosage forms of the drug.

In preferred embodiments, a drug/solubilizer solubilizing delivery system contains particles of a drug coated, at least partially, with a eutectic of the drug/solubilizer mixture. This product, upon ingestion, results in a blood plasma profile that indicates that the active is made available for uptake by the body much more quickly than drug alone would be available. In addition, the product is also able to deliver a larger amount of the drug than the eutectic alone. It is believed that during dissolution of the solubilizing delivery system the rapidly dissolving eutectic provides an initial amount of active followed by the solubilizer wetted particulate or crystalline form of the drug.

Detailed Description of the Invention

The invention relates to methods of making particulate active/solubilizer products by combining each ingredient under controlled temperature and processing conditions to yield particles of particulate (such as crystalline) actives coated with a eutectic of the active and solubilizer, and products comprising the particulate, eutectic coated solid active.

A eutectic is a combination of substances whose melting point is lower than that of any other combination of the same ingredients. Typically, eutectics melt at temperatures below the melting points of either individual ingredient.

Actives or active agents as used herein means any substance or material which one would like to improve the solubility or dissolution characteristics of. Pharmaceutical materials are the most preferred active. Such materials and ingredients will be readily apparent to the skilled artisan upon reading this invention.

In a preferred embodiment, a drug/solubilizer solubilizing delivery system of the invention, has a dissolution profile such that about 80%, or more of the drug will dissolve in water at pH 5.2 in about 5 minutes or less at 37 degrees C.

If the blend of ingredients is heated too far above the point at which the eutectic alloy forms, however, it is believed that crystals of the active ingredient dissolve in the solubilizer, or melt, resulting in a saturated or even a super saturated solution. Upon cooling the dissolved or melted active will then re-crystallize into crystals which are too large to benefit from the improved wetting of the solubilizer/eutectic coating and not dissolve as readily.

Generally, the method involves mixing from about 10% to about 95%, more preferably from about 30% to about 90%, and most preferably from about 40% to about 80% of particles of at least one active agent with from about 90% to about 5%, more preferably from about 10% to about 70%, and most preferably from about 20% to about 60% of at least one solid solubilizing agent (stabilizer) at temperatures from below the formation temperature of a eutectic of the drug/solubilizer mixture to below the temperature where the drug melts or dissolves in the solubilizer, and under sufficient forces to at least partially coat the particles of active with the eutectic material formed; and recovering the processed drug/solubilizer product. Optionally, the particle size of the recovered product can be further reduced according to known milling processes, for example. If milling or other particle size reduction methods are utilized care must be taken to insure that the temperatures created do not raise much above the original processing temperature or again, large crystals of active may form in the eutectic

The Ingredients:

A. Active Agents:

The active agent is a solid substance, preferably crystalline in nature, of generally poor water solubility. It is also preferable that the size of the particulate, or crystalline solid substance be small, preferably less than about 10 μ , with less than from about 6 μ being most preferred. The active agent is preferably a drug whose rapid dissolution and release is desirable, but whose solubility properties inhibit rapid dissolution. Among the useful drugs are analgesics, H₂ antagonists, non-steroidal anti-inflammatory agents, anti-cholesterolemics, anti-allergy agents and anti-migraine agents. Ibuprofen (IBP), Ketoprofen and Naproxen are especially preferred drug substances.

Other useful drugs include Dextromethorphan, Chlorpheniramine Maleate, 4-Acetamidophenol (APAP), Sodium Naproxen, Diphenhydramine, Diltiazem HCl, Cimetidine, and Fexofenadine. Any active agent, or drug which forms a eutectic with the solubilizer are contemplated as being usable and encompassed by this invention.

While the action of the processing equipment may cause some attrition, its is generally desirable that the drug be supplied in a finely divided state to facilitate formation of the eutectic and coating. Ideally, the particle size of the drug before processing will be less than about 10 μ , and preferably less than 6 μ .

B. The Solubilizer:

The solubilizers employed generally may have both a hydrophobic and hydrophilic (HLB) character. However an important characteristic of the solubilizing agent is its ability to form a eutectic with the material it is to be processed with. In general, the melting point of the solubilizer, or combination of solubilizers should be less than the melting temperature of the active. In addition, it is preferable that there be sufficient "head room" between the solubilizer melt temperature and the active melt temperature to enable one to process the combination at a temperature sufficiently low such that the active does not dissolve in the solubilizer. It is believed that if too much of the active ingredient dissolves in the eutectic, upon cooling the active will form crystals which will be so large that they cannot benefit from the wetting effects of the solubilizer and therefore, not dissolve as readily.

For some drugs, poloxamer surfactants are particularly useful. Polyoxyethylene/polyoxypropylene surfactants, such as the Pluronics/Lutrols made by BASF Corporation, are particularly effective. Pluronic or Lutrol F68 is especially preferred. Other useful surfactants include PEG-1000, PEG 2000 and the like.

5 For other drugs, useful solubilizers might be salts or other pharmaceutically acceptable compounds which form a eutectic and melt at temperature lower than the drug with which they are to be combined. Among these is urea.

It is preferred that from about 90% to about 5%, more preferably from about 10% to about 70%, and most preferably from about 20% to about 60% solid solubilizer be
10 utilized in the solubilizer delivery systems of the invention. Enough solubilizer must be present, in any event, to sufficiently coat or envelop the particles of active to enhance their dissolution.

C. The Method:

15 The method of the invention involves contacting solid particles of the active, including drug, and the solubilizer under conditions suitable to form the delivery system products of the invention. Following production of the products, the particulate product will generally be sized and employed, along with other pharmaceutical additives, in dosage forms.

20 Preferably the temperatures at which the ingredients are contacted are from below the formation point of the combination's eutectic to below the temperature at which the active will dissolve in the solubilizer so that the drug does not totally dissolve in the eutectic. When temperatures are too high, one or both of the ingredients can, upon cooling crystallize too quickly, resulting in crystal reformation which are too large to take
25 advantage of the wetting properties of the solubilizer/eutectic.

Typical temperatures used in the invention range from at or below the standard eutectic formation temperature to below the temperature at which the active melts or readily dissolves in the solubilizer utilized. It has been found by X-ray diffraction that upon cooling crystals of the active and solubilizer form in the eutectic material. These
30 crystals, however are very small unless the active is dissolved or present in the eutectic at too high a concentration. In addition, using the combination of temperature and force,

especially shear force, it is possible to form the eutectic and coat the particles of active at a temperature which is below the "normal" eutectic formation temperature at normal atmospheric pressure. It is also important for coating that the processing temperature be sufficiently high to control the viscosity of the mixture to allow for the forces to enable the coating of the active particles. For an Ibuprofen and Lutrol (Pluronic) F68 combination ,
5 preferred temperatures are from about 35 to about 45 degrees C.

If the temperature has to be kept low to prevent dissolving of the active, then it may be possible to encounter viscosity which makes coating difficult with an increase in the processing forces or through residence time of the materials in the presence of those forces.
10 The forces used during processing include but are not limited to centrifugal, shear and pressure. Shear and centrifugal forces are preferred. No matter what forces the materials are subjected to, however, the forces should be sufficient to coat the eutectic material onto crystals, or particles of the active. Generally the higher, or more intense or prolonged the forces, the more thorough the coating.

15 Additionally, sufficient amounts of ingredients must be used to sufficiently coat, or envelop the active particles or the enhanced dissolution properties will not be fully realized.

D. Devices:

20 The method of the invention is carried out on any device which provides the temperature and force conditions that facilitate eutectic formation and optional coating/encapsulation of the particles of active.

Suitable devices include extruders, flash flow spinning heads and the like. One highly preferred device is a multiple zone extruder having a length to diameter ratio L/D sufficient to coat or encapsulate particles of the active with the active/solubilizer eutectic material.
25

In addition, flash flow spinning heads are useful. Inside the device, the feedstock particles lose their resistance to liquid flow and become "liquiform." In this state, the eutectic is physically transformed from its original solid state, through a liquid state and back to a solid state instantaneously. While the particles undergo this transformation, they
30 are acted upon by centrifugal force, or another shearing force, which force separates them

into discrete eutectic coated particles. U. S. Patent _____, sets out the details of the liquiflash, flash flow processes.

The solubilizing delivery system particles may thereafter be ground by known methods such as milling and optionally screened to separate particles of a size sufficient
5 for the dosage form in which they will be included. The size reduction method should, however be monitored to prevent the delivery system particle from reaching temperatures above those used during their manufacture otherwise large crystal formation could occur. Once sized, the particles may be mixed with various pharmaceutical ingredients, e.g., sweeteners, fillers, perfumes, flow control agents, binders, and the like in suitable amounts.
10 Such dosage forms can include tablets and capsules and other oral dosage forms.

E. The Combination:

The active agent and solubilizer are to be combined in active:solubilizer ratios of about 95:5 to 10:90, preferably about 90:10 to about 25:75, most preferably about 80:20 to
15 about 40:60, with appropriate ratios being determined by the character of the ingredients. In general, it is preferred that the active ingredients be present in amounts that are as high as possible without detracting from the improved dissolution of the invention.

When IBP and the surfactant Lutrol (Pluronic) F68 are used in the inventive process, particles of IBP are coated (at least partially, and preferably completely) with a
20 eutectic mixture of the IBP and Lutrol F68. 80% of the solubilizing delivery system so produced will dissolve in 37°C degree water at a pH of 5.2 in five (5) minutes as measured by a Beckman/Hanson Automated Dissolution System as described below. The preferred ratios of IBP to Lutrol F68 are from about 60:40 to about 75:25.

It is believed that combinations of such additional drugs as Ketoprofen or Naproxen
25 and a solubilizer, or solubilizers such as Lutrol F68 with which they form a eutectic will be particularly useful.

While active agents such as drugs have been particularly discussed and are exemplified below, the invention encompasses any combination of ingredients where improved solubility or dissolution of one ingredient (the active) is beneficial. As indicated
30 the active must also form a eutectic with a solubilizer, or combination of solubilizers which

can be coated onto particles of that ingredient. Such materials and ingredients will be readily apparent to the skilled artisan upon reading of this invention.

Examples

The following examples illustrate the method and production of the novel products of the invention and are included as examples only and not intended to limit the scope of the invention.

Example I

Poloxamer 188 NF (Lutrol F68) was milled by passing the material through an Apex 114 mill with a 20 screen with the hammers forward. The feed rate was 4 RPM with a mill speed of 4590 RPM. The mill was allowed to cool for 15 minutes and then the material was run through again at the same settings.

9.76 kg of micronized Ibuprofen (IBP) and 6.60 kg of the milled Lutrol F68 were added to a Diosna V100 mixer in the following order: (1) one-half of the solubilizer, (2) all of the IBP, (3) the remaining portion of the solubilizer. The ingredients were mixed for about five minutes at speed II with the chopper off to produce a 60:40 IBP:Lutrol mixture. This mixture was used as a feedstock as follows:

The feedstock was fed to the spinning head disclosed in U. S. Application Serial No. 08/874,215, filed June 13, 1997. The head speed was increased to 60Hz while the heating elements were raised to a temperature which produced liquiflash conditions.

The spinning head forced the material through its orifices and the product was permitted to free fall a distance of from six to eight feet below the head. It comprises eutectic coated particles containing 60:40 IBP:solubilizer.

Example II

The same IBP/Lutrol F68 mixture as in Example I was made up as described in Example I. Instead of processing the mixture in a spinning head, however, an extruder manufactured by AVP was used as follows:

Set up the APV extruder with the water bath set to 20°C, and the heaters on and stable at 40°C. Fill the hopper with the IBP:Lutrol mixture and heat the exit orifice with a heat gun until a molten material is present.

Start the extruder at 50 RPM until the product is seen exiting the exit nozzle (~1 minute). Continuously feed the mixture until all temperatures are stable then set the RPM at 250.

Continuously process the material for 5 minutes then collect the product on plastic sheet lined trays.

Additional runs were conducted using extruders with different RPM rates, L/D (25 and 15) and with and without the exit nozzle in place (lower internal forces). These runs produced products where the particles of IBP were apparently not as thoroughly coated with the eutectic, or where the eutectic was not in as intimate a contact with the crystals of IBP as the product run with the higher L/D, slower RPM or with the nozzle in place. Dissolution test result, shown in Chart 1 below also support the requirement for sufficient force and low temperatures.

Example III

Extrudate Milling

Pass the extrudant through an Apex 114 Mill with no mesh and the hammers forward. Feed the mixture very slowly at a feed rate of 4 RPM and the mill at 4590 RPM and allow the top of the feeder to clear before continuing to feed. Care should be taken to not allow the milling process to generate too much heat.

Collect the milled material and pass it through the mill again using a No. 6 screen and the same settings. Again feed the hopper very slowly to avoid excessive heat and allow the top of the feeder to clear before continuing to feed.

Example IV

Ibuprofen Dissolution Studies

Microparticles of the milled extrudate and liquiflash formed IBP:Lutrol material of Examples I - III were tested for dissolution according to the following procedure. Some results are shown in Chart 1 below.

Instrumentation:

USP 711 Apparatus 2 (paddles), operated under the following conditions:

Speed:	50 RPM
Temperature:	37.0 ± 0.5°C
Medium:	PH 5.2 Phosphate buffer, 900ml

Sampling time: 5, 10, and 20 minutes

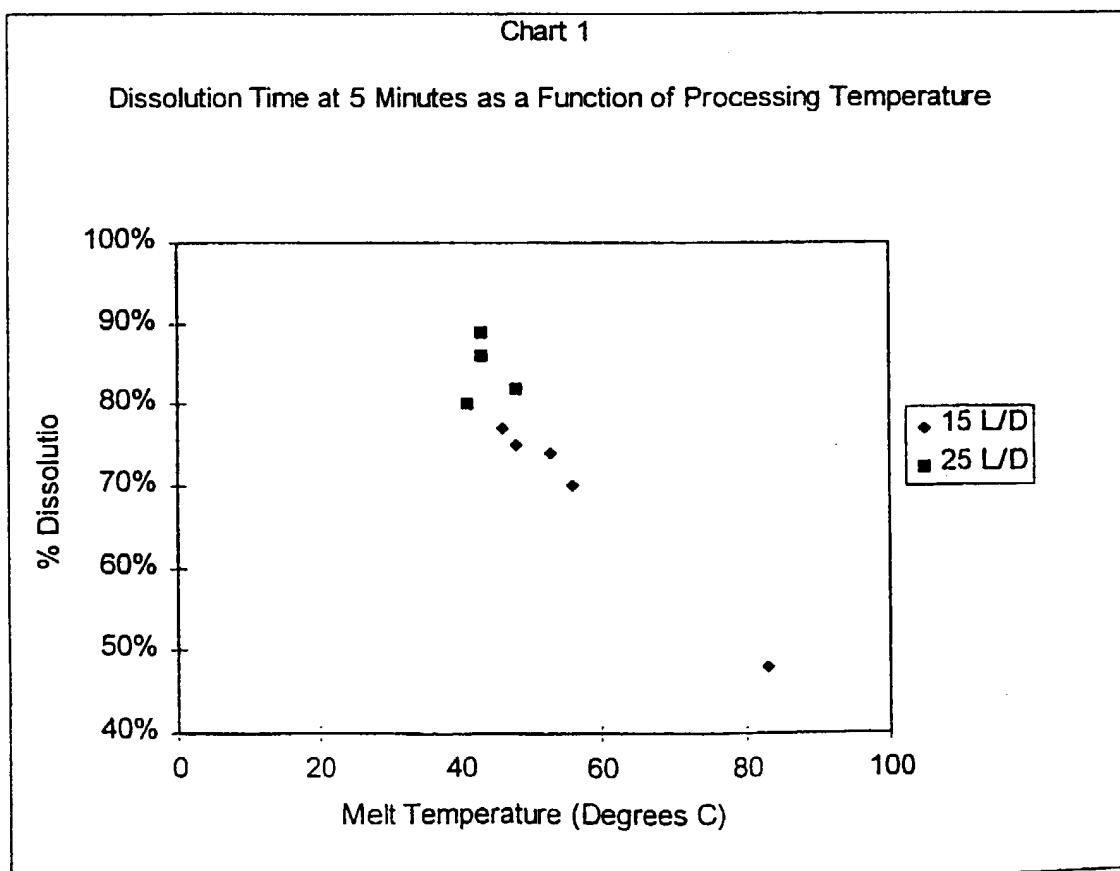
UV Spectrophotometer:

Wavelength: 266nm

Cell Pathlength: 1.0 cm

Procedure:

1. Dispense 900 ml of medium into each dissolution vessel.
2. Degas the medium by sparging with Nitrogen for 3 minutes.
3. Set up dissolution apparatus (Beckman/Hanson Automated
Dissolution System) by verifying the height of the paddles and equipping
sample probes with 10 micron pre-filters. Equilibrate the media to $37.0 \pm 0.5^\circ\text{C}$.
4. Weigh out enough sample to contain 200mg of IBP. Place a sample
in each vessel. Lower the apparatus to the appropriate level. Start the
apparatus at the above specified parameters.
5. At the specified times point the automated instrument will draw a
sample from each vessel and analyzer by the UV Spectrophotometer.



CLAIMS:

1. A method of making an active/surfactant solubilizing delivery system product the method comprising:
 - (a) mixing about 10 to about 95 parts of at least one particulate active agent
5 with about 90 to about 5 parts of at least one solid solubilizing agent;
 - (b) processing the mixture at temperatures from below the formation temperature of a eutectic of the active agent and the solubilizing agent to below the temperature at which the active dissolves in the solubilizer and under conditions of force and residence time sufficient to produce a eutectic of the active and solubilizer and to place
10 the eutectic in at least partial intimate contact with the particles of the active; and
 - (c) recovering the active/surfactant product produced.
2. The method of claim 1 which further comprises grinding or otherwise reducing the active/surfactant product into particles of a desired size.
15
3. The method of claim 1 wherein the particles of active and the solubilizer are mixed in a ratio of from about 30 parts to about 90 parts active and from about 70 parts to about 10 parts solubilizer.
- 20 4. The method of claim 1 wherein the particles of active and the solubilizer are mixed in a ratio of from about 40 parts to about 80 parts active and from about 60 parts to about 20 parts solubilizer.
5. The method of claim 1 wherein the active is a drug selected from the group
25 consisting of analgesics, H₂ antagonists, non-steroidal anti-inflammatory agents, anti-cholesterolemics, anti-allergy agents and anti-migraine agents.
6. The method of claim 5 wherein the drug is selected from the group consisting of analgesics.
30
7. The method of claim 6 wherein the analgesic is selected from the groups consisting of ibuprofen, ketoprofen and naproxen.

8. The method of claim 1 wherein the active is Ibuprofen (IBP) and the ratio of IBP to solubilizer is from about 60:40 to about 75:25

9. A solubilizing delivery system comprising particles of at least one active agent and at least one solubilizing agent in a ratio from about 10:90 to about 95:5, wherein the at least one active agent and the at least one solubilizing agent form a eutectic and the eutectic is in at least partial intimate contact with the particles of active.

10. The delivery system of claim 9 wherein the particles of active and the solubilizer are mixed in a ratio of from about 40 parts to about 80 parts active and from about 60 parts to about 20 parts solubilizer.

11. The delivery system of claim 9 wherein the active is a drug selected from the group consisting of analgesics, H₂ antagonists, non-steroidal anti-inflammatory agents, anti-cholesterolemics, anti-allergy agents and anti-migraine agents.

12. The delivery system of claim 11 wherein the drug is selected from the group consisting of analgesics.

13. The delivery system of claim 12 wherein the analgesic is selected from the group consisting of ibuprofen, ketoprofen and naproxen.

14. The delivery system of claim 13 wherein the active is Ibuprofen (IBP) and the ratio of IBP to solubilizer is from about 60:40 to about 75:25.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/19750

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category ²	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 02017 A (ELAN CORP PLC ;CLANCY MAURICE JOSEPH ANTHONY (IE); CUMMING KENNETH) 23 January 1997 cited in the application see page 5 - page 6 ----	1-14
Y	EP 0 349 509 A (PHARLYSE SA) 3 January 1990 see page 2, line 38 - page 4, line 4 ----- -/--	1-14

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.² Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 January 1999

Date of mailing of the international search report

16/02/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Seegert, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/19750

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
Y	<p>HAWLEY, A. R. ET AL: "Physical and chemical characterization of thermosoftened bases for molten filled hard gelatin capsule formulations" DRUG DEV. IND. PHARM. (1992), 18(16), 1719-39 CODEN: DDIPD8;ISSN: 0363-9045, vol. 18, no. 16, 1992, pages 1719-1739. XP000612180 see page 1724, paragraph 1 see page 1732 - page 1733 ---</p>	1-14
Y	<p>MURA, P. ET AL: "Solid dispersions of ibuprofen in urea. Effects of urea on dissolution" FARMACO, ED. PRAT. (1986), 41(12), 377-87 CODEN: FRPPAO;ISSN: 0430-0912, vol. 41, no. 12, 1986, pages 377-387, XP002091277 see abstract "Preparation of solid dispersions" see page 378 ---</p>	1-14
Y	<p>TANEJA, L. N. ET AL: "Solid dispersions of ketoprofen. In vitro characterization and bioavailability assessment" INDIAN DRUGS (1997), 34(2), 72-77 CODEN: INDRBA;ISSN: 0019-462X, vol. 34, no. 2, February 1997, pages 72-77, XP002091278 see abstract "Preparation of dispersion system" see page 75 -----</p>	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/19750

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9702017 A	23-01-1997	IE 80467 B	29-07-1998
		AU 6239496 A	05-02-1997
		CA 2226008 A	23-01-1997
		CZ 9704134 A	15-04-1998
		EP 0836475 A	22-04-1998
		NO 975872 A	03-03-1998
		SK 175997 A	03-06-1998
EP 0349509 A	03-01-1990	LU 87233 A	28-02-1990